

Initial Proposal for Core Hypotheses\Questions

I. Proposed Core Hypotheses/Questions

Hypothesis I: Prenatal Substance Exposure and Developmental Outcomes

Over time, prenatal exposure to drugs will interact with parent and child factors (e.g., genes, gender, mental and physical health, parent substance abuse, parent education); family characteristics (e.g., SES, race/ethnicity, culture, parenting style, parent involvement, structure); social networks and community involvement (e.g., peers, social support networks, spirituality, civic involvement, children's extra-curricular activities); and environmental factors (e.g., developmentally appropriate stimulation in the home, drug use and or toxins in home/neighborhood, access to and quality of child-care) to influence developmental processes and outcomes in cognitive, social/emotional and physical domains.

Hypothesis II: Youth Drug Use and Its Consequences

Initiation of drug use, transition to abuse and addiction, and physical and mental consequences of drug use are influenced by variables interacting over time, including parent and child factors (e.g., genes, gender, mental and physical health, parental substance use, parent education); family characteristics (e.g., SES, race/ethnicity, culture, parenting style, parent involvement, structure); social networks and community involvement (e.g., peers, social support networks, spirituality, civic involvement, children's extra-curricular activities); and environmental factors (e.g., developmentally appropriate stimulation in the home, drug use and or toxins in home/neighborhood, access to and quality of child-care).

II. Workgroup(s)

These hypotheses originate from the Development and Behavior Working Group (DBWG). It is anticipated that collaboration will occur across several working groups in further development of hypotheses and research questions.

III. Contact Person for Proposed Core Hypothesis\Question

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IV. Public Health Significance

A study prepared by The Lewin Group for the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism estimated the total economic cost of alcohol and drug abuse to be \$245.7 billion for 1992. Of this

cost, \$97.7 billion was due to the abuse of illicit drugs and other drugs taken for non-medical purposes (excluding nicotine). More than half of the estimated costs of drug abuse were associated with drug-related crime. Most of the remaining costs resulted from premature deaths (14.9 percent), lost productivity due to drug-related illness (14.5 percent), and healthcare expenditures (10.2 percent). Since 1990, estimates of drug-related visits to hospital emergency rooms have increased. In 1995, 531,800 drug-related visits occurred, up slightly from 1994. More than half of these visits were due to drug overdoses.

The White House Office of National Drug Control Policy (ONDCP) conducted a study to determine how much money is spent on illegal drugs that otherwise would support legitimate spending or savings by the user in the overall economy. ONDCP found that, between 1988 and 1995, Americans spent \$57.3 billion on drugs.

Substance abuse can have a major impact on the health and development of children and adolescents in a variety of ways – by exposure through maternal use during pregnancy, by growing up in a household where substances are abused, or by use of substances. It is estimated that 11% of U.S. children live with at least one parent who is either alcoholic or in need of treatment for illicit drug abuse (USDHHS, 1999). Of these 8.3 million children, 3.8 million are estimated to live with an alcoholic parent, 2.1 million with a parent who has an illicit drug problem, and 2.4 million with a parent who abuses both alcohol and illicit drugs. Estimates from a nationally representative sample of live births in U.S. hospitals indicate the following prevalence figures for substance use during pregnancy: 5.5% use of any illicit drug at least once during pregnancy, which translates to an estimated 221,000 pregnancies (NIDA, 1996). The marijuana estimate is 2.9% (119,000 pregnancies) and the cocaine figure is 1.1% (45,000 women). In addition, it was estimated that at some time during pregnancy 18.8% (757,000) of the women used alcohol, and 20.4% (820,000) smoked cigarettes.

At present, there are multiple in-progress cohort studies on developmental sequelae associated with prenatal exposure to illicit drugs. Data have generally shown subtle, but significant differences between exposed and non-exposed children on a variety of outcomes ranging from birth weight and birth head circumference to scores on tests of cognitive development (Lester, 1999). These subtle differences can have major public health significance, as discussed in a *Science* article (Lester, et al, 1998) on the potential impact of small differences in IQ and language test performance. Results of a meta-analysis led the authors to conclude that prenatal cocaine may not cause devastating brain damage, but it may possibly result in anatomical and molecular subtle brain damage, which could be the basis for the cognitive and language deficits observed. Based on the small differences in IQ seen in the data, the authors concluded that on a population basis, prenatal cocaine exposure could result in a significantly increased number of children who need special education services, at an estimated additional cost of up to \$352 million per year.

The Monitoring the Future Survey (MTF), conducted by the University of Michigan's Institute for Social Research and funded by the National Institute on Drug Abuse (NIDA), tracks a representative sample of 44,000 8th, 10th, and 12th graders in 424 schools across the nation and surveys their illicit drug use. In 2001, 26.8% of 8th graders, 45.6% of 10th graders, and 53.9% of 12th graders reported lifetime use of any illicit drug (i.e., at some time during their lives). Of all illicit drugs considered, marijuana use was reported most often by all 3 groups (20.4% of 8th graders, 40.1% of 10th graders, and 49% of 12th graders). Also notable, lifetime use of cigarettes was reported by 36.6% of 8th graders, 52.8% of 10th graders, and 61% of 12th graders.

According to the National Comorbidity Survey, a nationally representative study based on all relevant DSM-III-R criteria and conducted between 1990-1992 on persons 15 to 54 years of age, only a small subset of illicit drug users develop symptoms of Substance Use Disorder (SUD) (Warner, et al, 1995). Of the 51% of participants that reported lifetime illicit drug use, 14.7% met criteria for drug dependence. Generally speaking, dependence rates tend to be highest among 12 – 24 year olds and higher among men than women (Glanz, et al, 1999).

Prevalence figures such as those above speak to the public health significance of achieving greater understanding of the consequences of drug use initiation, ongoing use, and abuse. For example, available data indicate that the chronic use of drugs can result in long-lasting physical changes in the brain. These changes have been identified at molecular, cellular, structural, and functional levels (Hyman, 1996; Melega, et al, 1997; Nestler, 1996; Ortiz, et al., 1995; Volkow, et al., 1990). Furthermore, weaknesses in executive cognitive functions have frequently been found in individuals who abuse or are dependent on drugs (Giancola, et al, 1996). Despite a literature base on the topic, research has yet to clarify the extent to which these impairments precede or follow the exposure to drugs (Scheier & Botvin, 1996). Answers to questions such as this have implications for public health programs aimed at preventing drug abuse and ameliorating consequences of substance use and abuse.

V. Justification for a large, prospective, longitudinal study

The unique nature of this nationally representative longitudinal study will allow for a prospective investigation of (a) the effects of prenatal exposure to substances, and (b) pathways to drug use initiation, transitions to drug abuse and addiction, and mental and physical health consequences of substance abuse for important sub-populations of youth.

The number of variables and the complexity of relationships among the variables is the primary reason why a very large, longitudinal sample is needed to investigate these hypotheses. The large cohort will provide power for assessment of multi-factorial models, as well as the ability to examine crucial sub-samples of

the population. For example, it is likely that factors related to SES influence exposure and effects; however because prenatal exposure to substances has been studied primarily within lower SES populations, it has been difficult to detect these differences. A large sample size will allow detection of differences by SES level, as well as gender, race/ethnicity, and geographical location. The prospective longitudinal aspect of this study will allow for investigation of how developmental outcomes of prenatal substance exposure vary by substance, dosing, and timing of exposure. There are documented variations across geographical regions in primary drugs of choice, and in use patterns. These are but a few examples of the many factors that must be studied in their unique combinations, and the resultant need for a very large study sample that is drawn in a manner that enables examination of critical sub-samples.

In the case of prenatal exposure to drugs, except for one study on cocaine and opiate exposure (Bauer, et al, 2002), and one just getting underway on methamphetamine exposure, the multiple cohort studies in progress are single-sample investigations, with the resultant limitations of sample size. Even with the multi-site studies, sample size is still not sufficient to achieve the degree of sup-population analyses that are justified and needed, given the number and complexity of potentially important variables.

This design will also allow for the investigation of how youth behaviors and outcomes (among prenatally-exposed and non-prenatally-exposed youth), including initiation of drug use, transitions to drug abuse and addiction, and mental and physical health consequences of substance abuse, are influenced by interactions over time and reciprocity of interactions among child and parent factors, family characteristics, social networks and community involvement, and environmental factors. Furthermore, longitudinal studies are required for observing which factors influence development at critical periods, which factors have multiplicative effects after repeated exposures and/or interacting with other factors, and emerging latent effects (e.g., prenatal exposure effects observed during puberty).

VI. Scientific Merit

These hypotheses are supported by dynamic systems theory, which describes interdependent and transactional links among multiple factors, within an organism and across levels of an organism's environment, over time. The scientific outcomes of the proposed hypotheses will allow for a better understanding of (a) long-term developmental outcomes for children prenatally exposed to drugs and (b) developmental pathways to drug use initiation, abuse, addiction, and or consequences. This knowledge will substantially increase our ability to develop effective interventions, and ultimately, improve children's health and life quality.

Most research on child outcome relative to prenatal drug exposure involves cohort studies in which groups of children are followed longitudinally for varying

periods of time following birth. In a small percentage of studies, the sample is enrolled during pregnancy and/or fetal data are collected. As the field has evolved, studies have expanded from an emphasis on global developmental measures such as intelligence quotients (IQ) to more specific and subtle aspects of functioning, including measures of attention, arousal, emotional regulation, specific features of motor function, language, various aspects of problem solving, parent-child interaction, play, and behavior problems. Variations in the amount of information found in published studies, regarding important details such as sample selection, data collection methods, and attrition, complicates interpretation of findings and comparisons across studies. Furthermore, these studies are faced with the challenge of confounding factors associated with prenatal exposure. Prenatal drug exposure potentially may have both direct relationships with development (e.g., a specific aspect of biologic functioning) and indirect relationships resulting from the child's exposure to many associated factors (e.g., continued parental drug use and its related conditions).

The trajectories to drug abuse and addiction are complex and diverse and occur for a heterogeneous group of people. To date, there is no method for precisely predicting an individual's level of risk. However, there seems to be consistency in the finding that initiation of substance use at an earlier age is associated with greater likelihood of subsequent development of dependence (Anthony & Petronis, 1995; Grant & Dawson, 1998) and that the risk of drug abuse increases with the number and severity of prodromal risk factors (Bry, 1989; Maddahian, et al, 1988). Findings also suggest that involvement with drugs is typically hierarchical in nature, beginning with alcohol and/or cigarette use, and progressing to marijuana use followed by the use of other illicit drugs (Kandel & Yamaguchi, 1999). The majority of individuals at one step do not progress to the next. Little is known about the mechanism of sequence or the associations among these hierarchical steps. However, it is likely that these different steps are primarily influenced by different factors and different combinations of factors (e.g., Newcomb & Felix-Ortiz, 1992).

Recent research, using positron emission tomography (PET), has resulted in the identification of an association between the amygdala and drug cravings, which is strongly linked to the occurrence of relapse (Breiter, et al., 1997; Childress, et al., 1999; Volkow, et al., 1997). Further understanding of this link and associated environmental cues may prove to be very important in developing effective interventions to prevent or reverse the addiction process.

As noted earlier, the chronic use of drugs has been found to be linked to long-lasting physical changes in the brain, at molecular, cellular, structural, and functional levels (Hyman, 1996; Melega, et al, 1997; Nestler, 1996; Ortiz, et al., 1995; Volkow, et al., 1990). In addition, weaknesses in executive cognitive functions have frequently been found in individuals who abuse or are dependent on drugs (Giancola, et al, 1996). Large-scale, new studies can make important contributions toward clarifying the extent to which these impairments precede or

follow the exposure to drugs (Scheier & Botvin, 1996), toward understanding the specific nature of exposure-outcome relationships, and consequently toward providing directions for interventions.

VII. Potential for innovative research

The most innovative aspect of research on these two hypotheses (and an aspect achievable only in a very large longitudinal study such as the National Children's Study) is the ability to conduct the most thorough and definitive work possible on the complex issues reflected in the hypotheses. As noted above, even with multi-site studies that do exist, it is not possible to achieve the degree of sub-population analyses needed. Furthermore, the NCS will allow intensive investigation of mechanisms (biological, genetic, and social environmental) that may underlie associations between exposure and outcomes. It will also be novel in permitting simultaneous examinations of relationships of different drugs and drug use patterns to outcomes while using the same methodology (e.g., study of the same health and development markers following prenatal methamphetamine exposure in some regions of the country and prenatal cocaine in other regions; study of comparable health and development indicators associated with inhalant use among some youth and marijuana use among others).

Among other innovative aspects will be the contribution of "norms" on many of the measures used to assess health and development in the children (and to assess family and environmental factors). The resulting "norms" will exceed those available even for standardized tests and measures used in the study. This is something that will be true for many components of the NCS. In the case of these specific hypotheses, "norms" will be developed on numerous measures by virtue of the need to examine a range of health and development status indicators. These "norms" can be used in other research, and should be available shortly after each wave of assessment.

It is also likely that new technologies will be developed and/or refined in conducting the research on these hypotheses. Possibilities include improved methods for detecting drug exposure in infants, new and enhanced ways of determining drug use among youth of varying ages, and refinement of specialized pediatric neuroimaging procedures and analytic approaches.

VIII. Feasibility

In the case of Hypothesis I, a major 'critical period' for exposure to drugs is the entire in utero timeframe. In addition, critical times of exposure within the in utero period may be expected to have varying implications for different domains of outcomes (e.g., organogenesis, birthweight, head circumference, cognitive function). Critical times for outcomes relative to prenatal drug exposure are multiple, ranging from the fetal period into infancy and throughout childhood and adolescence. Current literature indicates that the manifestation of differences

between exposed and non-exposed children may occur at different times as a function of domain of outcome, and in some cases may be seen to occur as a ‘sleeper effect’ (e.g., an outcome not evident until the child is challenged by school-related demands).

For Hypothesis II, important periods occur throughout late childhood, adolescence, and young adulthood, for both exposure and outcome variables. For example, initiation of drug use may occur for some children quite early in life, whereas others will start experimentation and use much later. The interaction of variables contributing to drug use/abuse at a given age are likely to differ from the combination occurring at another age, and the consequences of use/abuse at one age are likely to be different than those at another age.

Sampling for both hypotheses will involve targeted groups and settings. Multiple contacts will be necessary for the investigation of both hypotheses. The timing of assessments are likely to be frequent early in life, less frequent during the early school years, and then increasing in frequency at pre-adolescence and early adolescence, periods of biological and social transition. Measurement tools for assessing exposures and outcomes will involve a wide range of methods: specimen assays, medical diagnoses and clinical assessments, interviews, questionnaires, and a variety of neurodevelopmental and psychological tests (both standardized and laboratory-based procedures).

As is evident from the above, recruitment, sample retention, and assessment strategies will be complex. However, experience to date is extensive in all aspects of the proposed research. The measures likely to be utilized have been employed in multiple studies. Relevant logistical issues have been addressed in multiple studies (e.g., demands made on infrastructure by having to test large numbers of children in clinical care and school systems; timing of assessments and participant burden; coordinated testing of children and family members). Success and efficiency in screening large numbers for study recruitment (using questionnaire and biological specimen measures) have been documented. For example, in one multi-site study of prenatal cocaine and opiate exposure (Bauer, et al, 2002), 19,000 mother-infant pairs were screened. A similar number will be screened in a newly-started prenatal methamphetamine exposure study. Effective training on recruitment and assessment techniques has occurred in multiple large studies. Data management systems have been established and proven effective. Furthermore, topics such as those reflected in Hypotheses I and II have required careful consideration of a variety of human subjects issues, such as use of Certificates of Confidentiality, child assent, and parental consent with explication of legal and ethical reporting requirements; multiple studies have successfully addressed these and similar issues.

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